Toy amphiphiles on the computer: What can we learn from generic models?

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Summary:
Generic coarse-grained models are designed such that they are (i) simple and (ii) computationally efficient. They do not aim at representing particular materials, but classes of materials, hence they can offer insight into universal properties. Here we review generic models for amphiphilic molecules and discuss applications in studies of self-assembling nanostructures and the local structure of bilayer membranes, *i. e.,* their phases and their interactions with nanosized inclusions. Special attention is given to the comparison of simulations with elastic continuum models, which are, in some sense, generic models on a higher coarse-graining level. In many cases, it is possible to bridge quantitatively between generic particle models and continuum models, hence multiscale modeling works on principle. On the other side, generic simulations can help to interpret experiments by providing information that is not accessible otherwise.

Keywords: amphiphiles; block copolymers; lipids; phase diagrams; membranes; micelles; modeling; simulations; elastic theory

1. Introduction

Amphiphiles are key constituents of living matter and of many technologically important substances and materials.[1–3] In the literal sense, the term "amphiphile" describes a chemical compound containing hydrophilic as well as hydrophobic parts. More generally, it is used for compounds where chemically incompatible units are permanently linked together, such as block copolymers. Amphiphiles are highly surface active, *i.e.*, they segregate to interfaces and surfaces and alter their interfacial properties. At high amphiphile concentrations, amphiphilic substances have a propensity to "microphase separate", *i. e.,* to develop complex structures on the mesoscale that contain many internal interfaces. As an example, consider lipids, a particularly prominent class of amphiphilic molecules. They are made of one

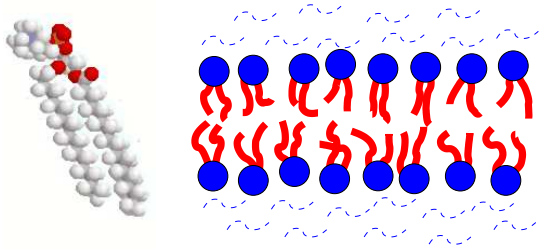

Figure 1: Left: Example of a lipid molecule (DPPC). Right: Schematic sketch of a lipid bilayer.

polar (hydrophilic) head group connected to two or more nonpolar (hydrophobic) tails (see Fig. 1 a). In water solution, they self-assemble into a variety of nanostructures, *e. g.,* micelles, vesicles, sponges, or lamellae. Many of these structures share as common element the lipid bilayer, a stack of two opposing lipid monolayer sheets, where the lipids are arranged such that the hydrophobic tails are shielded from the water by the hydrophobic heads (Fig. 1 b)). Lipid bilayers play a central role in biophysics, since they provide the basic frame for biomembranes.[4,5]
Amphiphilic systems exhibit two particularly striking features, which have attracted theoretical interest for many decades: The *self-assembly* of molecules into complex structures, often associated with mesophase formation, and very peculiar *interfacial properties*, both for interfaces that separate macrophases and for interfaces that are part of a mesophase (as in the case of membranes). Traditionally, theorists have taken different routes to describe these different aspects of amphiphilic systems. While the self-assembly and mesophase formation is usually treated within approaches based on bulk thermodynamics, *e. g.,* packing arguments,[2] or (bulk) field theories of varying complexity,[1,6] the interfacial aspects have often been discussed in terms of "effective interface" theories, where the essential degrees of freedom are assumed to be localized on effectively two-dimensional manifolds, the interfaces.[7] The most famous example of an effective interface Hamiltonian is the "Helfrich Hamiltonian", introduced by Helfrich[8] in 1973, which relates the free energy of bilayer membranes to the invariants of their local curvature tensor,

$$\mathcal{H} = \int \mathrm{d}A\{\sigma + 2\kappa(H - c_0)^2 + \frac{1}{2}\bar{\kappa}K\}. \tag{1}$$

Here $H = (c_1 + c_2)/2$ (mean curvature) and $K = c_1 c_2$ (Gaussian curvature), with the principal curvatures c_1 and c_2 (*i. e.,* the Eigenvalues of the curvature tensor). The Helfrich Hamiltonian involves four phenomenological parameters, the surface tension σ, the bending modulus κ, the saddle-splay modulus $\bar{\kappa}$, and the spontaneous curvature c_0, which depend on the molecular structure of the membrane. Bulk

membranes at equilibrium should be tensionless ($\sigma = 0$), and symmetric bilayers should not have a spontaneous curvature ($c_0 = 0$). Moreover, the contribution of the Gaussian curvature is a constant for closed surfaces with fixed topology. This leaves one with only one parameter κ in the simplest case. The Helfrich Hamiltonian is often used as starting point for more complex elastic theories of monolayers and bilayers, which incorporate additional factors such as the membrane thickness, internal degrees of freedom, interlayer coupling etc.

The third route to studying amphiphilic systems is of course the use of computer simulations. Since simulations in full atomic detail are very expensive and the system sizes accessible for such simulations are still limited, coarse-grained models are widely applied to investigate various aspects of amphiphilic systems. Two different coarse-graining philosophies have been pursued, *systematic* coarse-graining and *generic* coarse-graining. In the first approach, coarse-grained models are derived more or less systematically from atomistic models. The vision is to develop strategies for constructing whole hierarchies of coarse-grained models for specific materials, which can then be used to make quantitative predictions of material properties.[9–12] In the second coarse-graining line, idealized models are developed which incorporate only properties of amphiphiles that are deemed essential for their particular behavior. Such "generic" coarse-grained models are less quantitative than systematic coarse-grained models, but they give insight into basic physical mechanisms which are responsible for the peculiar properties of amphiphiles, and they can make predictions for whole classes of materials. Generic coarse-graining has a long-standing tradition in the theory of amphiphilic systems; the earliest model, the Wheeler-Widom model (a simple Ising-type lattice model) dates back to 1968.[13] Nowadays, a whole zoo of lattice and off-lattice models has been proposed and used to study various aspects of amphiphilic systems. Discussing them all is far beyond the scope of this article. A number of review articles have appeared that provide an overview over coarse-grained models for self-assembling amphiphilic systems in general[1,14–16] or for membranes in particular.[17–21] Here, we shall solely give examples, mainly from our own work.

In the next section, we discuss equilibrium and dynamical aspects of amphiphile self-assembly on mesoscopic scales – the traditional realm of generic amphiphile models. In section three, we examine bilayer membranes on a more local scale, most notably, internal membrane phase transitions. Even on this scale, generic models can provide valuable insights into basic processes that govern membrane

(bio)physics. We conclude with a brief outlook in section four.

2. Self-assembly and mesoscale structure

Modeling

Most generic models that have been used to simulate amphiphile self-assembly and mesostructure formation in amphiphilic systems belong to one of three categories: Lattice spin models[22–26] particle models,[27–33] and field-based models – the latter may be purely phenomenological[1] or derived from (coarse-grained) molecular models.[18] Here we will discuss particle- or field-based models with an underlying particle picture. These models have in common that they identify as crucial factor the amphiphilic character of the molecules, *i. e.,* the fact that they are made of two chemically incompatible blocks.

The central idea of generic coarse-graining is to restrict the description of a system to bare essentials, *i. e.,* to simplify as much as possible. One particularly simple computer model for self-assembling amphiphiles has been proposed in 1990 by Smit *et al.* [30,31] and has since become an archetype off-lattice model for amphiphilic systems. (An analogous, similarly successful chain model on a lattice had been introduced five years earlier by Larson.[27]) The basic elements are beads, which may have one of two types, w (water-like) or o (oil-like). The interactions between beads are chosen such that w beads and o tend to segregate. Amphiphilic molecules are represented by chains of w and o beads. This model produces micelles and bilayers – indicating that the amphiphilic character of molecules is indeed sufficient to drive self-assembly.

A second more practical requirement for generic computer models is computational efficiency. Since the details of the potentials are usually not in the focus of interest, they may as well be chosen such that computer simulations are cheap. In recent years, a number of models that are very interesting from this point of view have been developed at the Max-Planck Institute for polymer science in Mainz. Soddemann *et al.* [34] have designed a Smit-type model which is optimized such that the basic bead structure is largely that of a simple hard sphere liquid, independent of the overlying oil/water/amphiphile "colouring". To this end, the range of attractive interactions and the molecular bond length are chosen such that they match the interparticle distance in the liquid. Length scale frustrations that slow down the simulations are thus avoided; moreover, semi-grandcanonical Monte Carlo identity switches are facilitated considerably. The Soddemann model and variants thereof have been used to study structure formation in amphiphilic systems under equilibrium and nonequilibrium conditions.[35–43] Another, even cheaper model that is specifically designed to study large scale properties of bilayers has recently been

proposed by Cooke *et al.* .[44] Amphiphiles are represented by chains of three beads (one w, two o), and because of a smart choice of potentials, the solvent (water) can be omitted altogether. From the point of view of computational efficiency, implicit solvent models are of course particularly appealing, and numerous studies had shown that they are suitable to study self-assembled structures in binary amphiphile/water systems.[45–51] As an alternative to implicit solvent models, we have proposed a "phantom" solvent model, where the solvent only interacts with lipids.[52,96] In Monte Carlo simulations, which is only slightly more expensive.

The most optimized particle-based models for amphiphilic systems, represent amphiphilic molecules by just a few elementary units ($\sim$ 2-4 beads). Such descriptions are highly successful for short-chain amphiphiles. In the case of (co)polymeric amphiphiles, however, the chain character of the molecules may become important, and coarse-grained models should incorporate this aspect. Therefore, particle-based simulations of polymeric amphiphiles have often resorted to using established coarse-grained polymer models, such as the bond-fluctuation model,[53] or similarly popular off-lattice models.[54] Unfortunately, simulations of long-chain polymeric systems at high densities are expensive even with the most optimized particle-based polymer models. This motivates the use of field-based models that propagate density fields (or related fields) instead of particles. Such models can be derived more or less systematically from a chain molecule picture *via* a route borrowed from one of the most successful polymer mean-field theories, the self-consistent field (SCF) theory.[55–57] In the SCF approximation, systems of interacting chains are replaced by an ensemble of independent chains in an inhomogeneous field, which is determined self-consistently. Already early applications of this approach have dealt with amphiphilic systems, *e. g.,* it has been used to study micelle structures[59] or microphase separation in block copolymer melts.[60,61] Compared to particle-based simulations of block copolymer/homopolymer mixtures, SCF theories can reproduce local structures at a *quantitative* level,[62,63] provided that one identifies the correct "intrinsic coarse-graining length".[64] More recently, methods to include dynamics[65–68] and fluctuations beyond mean-field[69–71] have been developed. Together, these methods constitute the new class of "molecular field-based" (or "field-theoretical") simulation methods for polymeric systems. The derivation of field-based simulation models is complicated and technical and shall not be presented here. The interested reader is referred to recent reviews.[72,73]

After this brief and highly incomplete review of approaches to modeling amphiphile self-assembly on "large" scales (*i. e.,* nm to μm range) at a generic level, we proceed to presenting actual simulation studies from our group. We shall ask two questions: (i) To which extent can elastic theories such as the Helfrich theory (1) describe the properties of self-assembled amphiphilic systems, and (ii) how do amphiphiles self-

assemble in practice, *i. e.,* , which are the kinetic pathways of self-assembly?

Fluctuating mesoscale structures versus elastic theory

In order to address the first question mentioned above, we have used a generic particle-based model which exhibits swollen lamellar phases, and compared the properties of the structures observed in the simulations with the predictions of appropriate continuum theories. Specifically, we have used a variant of the Soddemann model,[34] where amphiphilic molecules are represented by w_2o_2 tetramers and dissolved in w solvent. At sufficiently low temperatures, the systems develops a lamellar phase. We found that the lamellae can incorporate roughly 40 volume % solvent without being destroyed. The simulations were carried out at 20 % solvent. A snapshot is shown in Fig. 2 (left). The system has a relatively high degree of order, but thermal fluctuations and membrane defects are still prominent.

According to the simplest elastic model,[74] the free energy of a lamellar stack is given by

$$\mathcal{H} = \sum_n \int \mathrm{d}A \{ \frac{\kappa}{2} (\Delta u_n)^2 + \frac{B}{2} (u_{n+1} - u_n)^2 \}, \tag{2}$$

where $u_n(x, y)$ denotes the local deviation of the height of the nth lamella from its average value, κ is the bilayer bending modulus introduced earlier (1), and B the compressibility of the stack. This free energy determines the amplitude of thermal fluctuations of the lamellar position u_n. As an example, we consider the "transmembrane structure factor" $S_n(q_x, q_y) = \langle u_n(\mathbf{q}) u_0(\mathbf{q})^* \rangle$, which can be calculated analytically[38] ($u_n(\mathbf{q})$ is the two-dimensional Fourier transform of $u_n(x, y)$). Fig. 2 (middle) shows a comparison between theory and simulation, with only one fit parameter $\xi = (\kappa/B)^{1/4}$. The agreement is excellent.[38]

A similarly simple free energy model for pore defects in membranes, where the statistics of pore shapes is taken to depend only on the line tension, was found to perform equally well in comparison with the simulations.[39] Even the behavior of long polymers inserted in the membrane can be understood by scaling arguments that are based on the elastic theory of membrane stacks (hydrophilic polymer collapse and create exactly one pore).[40]

We conclude that our generic simulations confirm the validity of elastic models for the description of fluctuating amphiphilic bilayer systems on the mesoscale. We shall see later that they even perform surprisingly well on the scale of the membrane thickness.

Kinetics of self-assembly

Our second question relates to dynamical aspects of self-assembly. Here, we were particularly interested in the pathways leading to the formation of amphiphilic

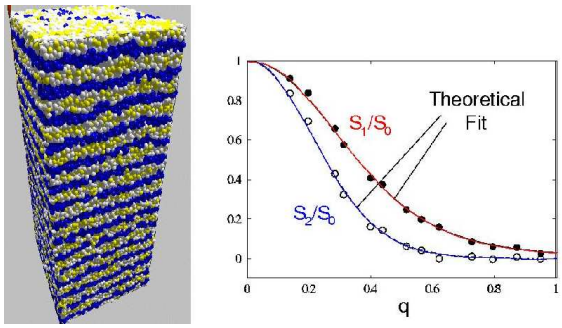

Figure 2: Left: Snapshot of a lamellar stack from a coarse-grained simulation of $w_2 0_2$ amphiphiles with 20 % o-solvent. Right: Transmembrane structure factor for this system vs. in-plane wavevector q (arbitrary units), compared with elastic theory. See text for explanation. (from Ref. 38).

copolymeric vesicles or other self-assembled copolymeric nanostructures. The work was motivated by increasing recent experimental interest in these structures.[75–80] Artificial vesicles are expected to have a high potental in nanotechnology as microreactors or microcontainers. Since it may take weeks or months before vesicle solutions are truly equilibrated, the vesicles observed in experiments are often nonequilibrium structures which depend on the history of the system, *i. e.,* on the kinetic pathways of self-assembly. These pathways are hard to unravel experimentally, hence computer simulations can provide useful insight.

Previous simulation studies of vesicle self-assembly have revealed one possible pathway to vesicle formation (hereafter referred to as pathway I): In a first step, small micelles form; then, the micelles coalesce to disks, *i. e.,* small bilayer fragments; finally, the disks curve around and close up to form vesicles. These simulations focussed on short-chain amphiphiles.[29,81–85] In copolymeric amphiphiles, the local driving forces for segregation are weaker and the diffusion is slower. The question was whether this has an effect on the pathway and the final self-assembled nanostructures.

To study this problem, we used a coarse-grained field-based model, the "external potential dynamics" (EPD) method developed by Maurits and Fraaije in 1997.[67] We study an underlying particle model where amphiphiles are represented by linear strings ("Gaussian chains") with a short hydrophilic block A attached to a longer hydrophobic block B (length ratio 2:15), immersed in a solvent S. In EPD, the chains are taken to propagate in their surrounding self-consistent field according to "Rouse dynamics",[86] *i. e.,* the effect of chain connectivity is accounted for, but entanglements and hydrodynamic effects are neglected. The system is characterized

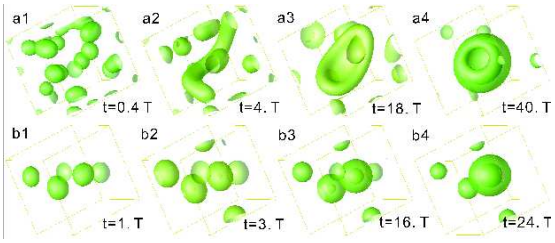

Figure 3: Pathways of spontaneous vesicle formation in copolymer solutions. Top: Pathway I observed at a copolymer volume fraction of 20 % with (a1) micelle formation, (a2) micelle coalescence, (a3) bilayer formation, and (a4) bending into vesicle. Bottom: Pathway II observed at a copolymer volume fraction of 15 % with (b1) micelle formation, (b2) micelle growth, (b3) internal reorganization into semivesicle, and (b4) swelling into vesicle. From Ref. 89.

by three interaction parameters χ_{AB}, χ_{AS}, and χ_{BS}, which describe the mutual incompatibility of A chain segments, B chain segments, and the solvent S (the larger χ_{ij}, the more incompatible i and j). Of these, the parameter χ_{BS} turned out to be the most influential, hence the other two were kept fixed. Another important quantity is the volume fraction Φ_p of copolymers.

The simulations revealed that spontaneous vesicle formation from homogeneous solution may in fact proceed *via* two distinct pathways (see Fig. 3). At high copolymer concentrations Φ_p, we recover the "traditional" pathway I described earlier, including micelle coalescence, sheet formation, and sheet bending (Fig. 3, top). At low copolymer concentrations, a new pathway is observed, which is characterized by growth processes rather than aggregation (pathway II). Here the first step is micelles formation as in pathway I, but instead of coalescing, the micelles then keep growing by incorporating more and more copolymers from the solution until the radius of the hydrophobic core exceeds the radius of gyration of the B block. Then, copolymers start flipping such that the micelle core becomes hydrophilic ("semivesicle state"). Finally, solvent diffuses inside the core, and the semivesicle swells to form a vesicle.[87]

This second pathway turns out to be auspicious, as it can be exploited to manipulate the sizes and shapes of self-assembled nanostructures. For example, the final size distribution of vesicles can be influenced by mixing seeds into the initial homogeneous solution.[88] At low copolymer concentration, the vesicles developing from such seeds may develop hierarchical multicompartment structures.[88] Even in the absence of seeds, micelles with complex toroidal or net-cage structures may form at low copolymer concentrations close to the CMC (critical micelle concentration).[89] A dynamical "phase diagram" of final structures after a quench from homogeneous

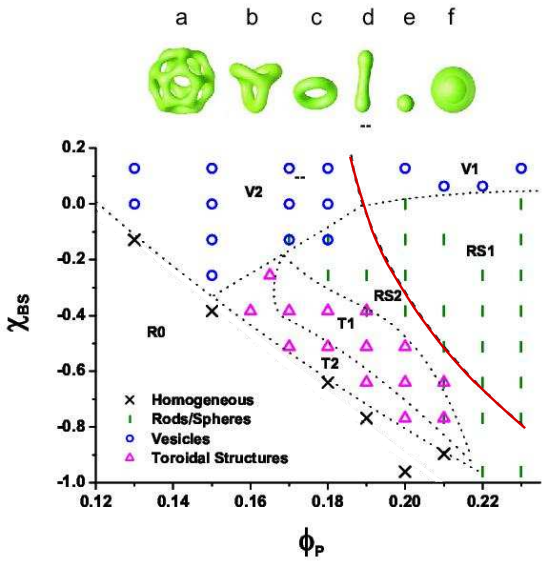

Figure 4: "Phase diagram" of final structures after a quench from an initially homogeneous A : B-copolymer solution for a range of B-Solvent interactions χ_{BS} and copolymer volume fractions Φ_p. The final structures in the regions V1/V2 correspond to vesicles (f), RS1/RS2 to rod-sphere mixtures (d,e), T1 to ring micelles (c), and T2 to toroidal micelles (b,a). In the region R0, the solution stays homogeneous. The solid line separates two dynamical regions where the structure formation proceeds along pathway I (regions RS1 and V1) and pathway II (regions RS2,T1,T2,V2). The dotted lines are guides for the eye. After Ref. 89.

solution (no seeds) is shown in Fig. 4.
The simulations covered length scales in the μm range and time scales up to almost one second. Such length and time scales are difficult to access with particle-based models, let alone atomistic models. They demonstrate the power of field-based simulation methods to unravel basic mechanisms of self-assembly. The simulations can not only help to understand experiments, they may also be used to guide them, *e. g.,* in order to produce certain types of nanostructures in a controlled way.

3. Membrane structure

Lipid membranes

In the second part of this paper, we discuss the value of generic models for studying internal properties of lipid membranes, *i. e.,* structural properties on length scales of the membrane thickness d or just a few d ($\sim 100d$). Unlike for mesoscale

structures, it is far from obvious that generic models are of any use here. One might rather suspect that the membrane properties on such small scales are dominated by specifics of the molecular structure of the constituting lipids. On the other hand, experimental bilayer studies for a wide class of lipids indicate that the behavior of membranes is to a large extent dictated by universal, nonspecific factors.[90,91]

At high temperatures, lipid bilayers usually assume a "fluid" state which is characterized by a relatively high lipid mobility, low shear viscosity, and a high degree of disorder in the lipid tails, the L_α phase. Upon decreasing the temperature, one encounters a so-called "main" transition to a more ordered "gel" state with lower mobility. The characteristics of the low-temperature phase are mostly determined by the geometry of the lipids. For lipids with small head group volumes such as, *e. g.,* phosphatidylethanolamines, chains in the gel state are on average untilted with respect to the bilayer normal (the L_β phase). Lipids with larger head groups such as, *e. g.,* phosphatidylcholines, usually assume a gel state where the lipids exhibit collective tilt (the $L_{\beta'}$ state). In some cases, where the head-head attractions are weak, they may also form an untilted L_β^{int} state where opposing lipid layers are fully interdigitated. These observations seem to be quite universal, which raises the hope that the basic characteristics of the main transition can be reproduced by suitable generic models.[92,93]

The main transition from the fluid state L_α to the tilted gel state $L_{\beta'}$ is particularly intriguing, because it actually proceeds in two steps. There exists an intermediate phase $P_{\beta'}$, first discovered by Tardieu in 1973,[94] which is characterized by periodic stripe modulations. This so-called "ripple" phase has been studied intensely with various methods, *e. g.,* calorimetry, atomic force microscopy, NMR, and extensive X-ray measurements, but nevertheless, it has not yet been possible to determine the exact microscopic structure by experiments. We shall see that generic computer simulations can be of use here.

It is clear that the optimized amphiphile models discussed in the previous section are too simple to be a good starting point for studies of internal membrane transitions. Theoretical mean-field calculations[95] indicate that the main transition is driven by an interplay between the conformational entropy of the tails and their tendency to develop nematic order, hence a good model should take into account the chain character of lipids. Our membrane model[96] is based on an amphiphile model that has already been used successfully to study phase transitions in Langmuir monolayers[97–103] The lipids are modeled by semiflexible chains of 6 "tail" beads attached to one slightly larger "head" bead. Tail beads attract each other, whereas head beads are purely repulsive. This drives a local segregation of heads and tails. In addition, a fluid of "phantom solvent" beads drives the self-assembly of lipids into membranes (see above[52]).

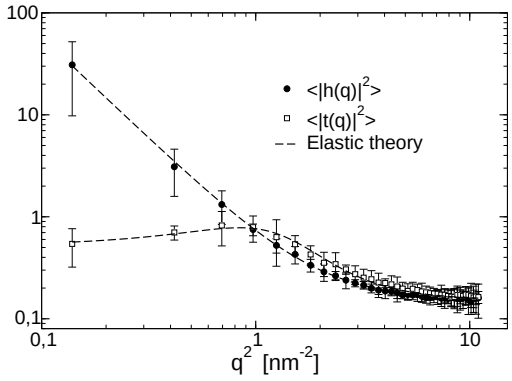

Figure 5: Fluctuation spectrum of height and thickness fluctuations of a planar membrane, simulated with our generic membrane model,[96] compared with the elastic theory of Brannigan and Brown.[105] Here $h(\mathbf{q})$ and $t(\mathbf{q})$ are the Fourier transforms of the local mean position and monolayer thickness of the membrane, $h(x,y) = (z^+(x,y) + z^-(x,y))/2$ and $t(x,y) = (z^+(x,y) - z^-(x,y))/2$, where $z^+(x,y)$ and $z^-(x,y)$ are the local positions of the opposing head group layers. After Ref. 106.

Like real phosphotidylcholine bilayers, the model exhibits a fluid L_α phase at high temperatures and a tilted gel $L_{\beta'}$ phase at lower temperatures.[104] We have examined in detail the properties of fluid membranes at a temperature slightly above the main transition. They turn out to be surprisingly 'realistic'. The ratio of area per lipid and squared monolayer thickness roughly corresponds to that of DPPC bilayers (~ 0.16). We thus use the properties of DPPC bilayers to map our intrinsic model units to SI units – more specifically, we match the bilayer thickness and the temperature of the main transition to identify the length and energy scale in our system. The elastic parameters of the membrane can be determined from the stress tensor profile across the membrane[7] and from an analysis of membrane height and thickness fluctuations. We use as reference an elastic theory due to Brannigan and Brown,[105] which treats membranes as a system of two coupled elastic monolayer sheets and also accounts for protrusions. Fig. 5 shows that this theory fits the simulation data excellently.[106] The resulting elastic parameters κ (bilayer bending modulus), k_A (area compressibility), and c_0 (spontaneous curvature of the monolayer) are given by $\kappa \approx 2.2 \cdot 10^{-20}$J, $k_A \approx 130$mN/m, and $c_0 \approx -0.08$/nm. In comparison, experimental values for DPPC are[107] $\kappa \sim 5 - 20 \cdot 10^{-20}$J and $k_A \sim 230$mN/m, and values from fully atomistic simulations are $\kappa \sim 4 \cdot 10^{-20}$J,[108] $k_A \sim 300$ mN/m,[108] and $c_0 \sim (-0.02) - (-0.05)$/nm.[109] Our simple generic membrane model thus not only recovers general the elastic behavior of fluid membranes,

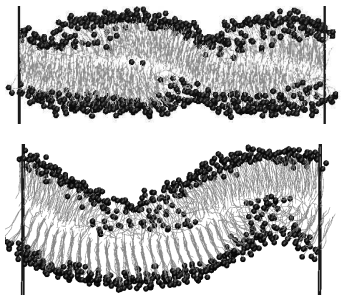

Figure 6: Two snapshots of ripple states in our generic membrane model. Only heads (reduced size) and tail bonds are shown. Top: Asymmetric ripple state, obtained after cooling rapidly from the fluid L_α state. Bottom: Symmetric ripple state, obtained after cooling slowly from the fluid L_α state. After Ref. 104.

but the material constants even have the correct order of magnitude. This suggests that the range of elastic constants is to a large extent determined by generic factors.

These results are already rewarding. The biggest success of our generic model, however, is that it recovers the modulated intermediate phase between the fluid L_α phase and the lower temperature $L_{\beta'}$ phase, which is observed in real lipid membranes. The intermediate state reproduces many features of the experimental $P_{\beta'}$ (ripple) state: There exist two modifications, one which is asymmetric and one which is symmetric with twice the period of the asymmetric structure[110, 111] – both structures are observed in simulations (see snapshots in Fig. 6). As in experiments, the asymmetric state is observed after cooling rapidly from the fluid L_α state or heating from the $L_{\beta'}$ state, and the symmetric state is observed after cooling slowly from the fluid state. In both ripple states, most of the chains are highly ordered, much like in the gel state. The self-diffusion of lipids, on the other hand, is significantly higher than in the gel state, and highly anisotropic, suggesting that ripple states contain anisotropic "coexisting" gel-state and and fluid-state domains. Indeed, such ordered and disordered stripes can clearly be identified in the simulations.

It is worth noting that the asymmetric ripple state does not have a structure involving two distinct monolayers. In this respect, it differs fundamentally from the structures of the two neighbor phases, the L_α and the L_β phase, and also from cartoons of the ripple-phase that are typically found in textbooks.[4] On the other hand, a similar structure has recently been observed in an atomistic simulation of lecithin bilayers.[112] Our coarse-grained simulations indicate that this structure is generic, lipids do not need to have special properties to produce it. In particular,

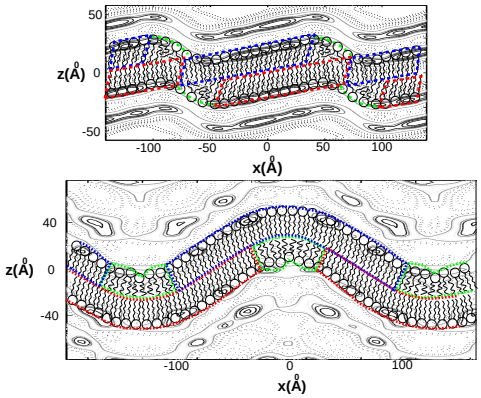

Figure 7: Structure proposition for ripple states superimposed onto EDMs from Ref. 113. Top: Asymmetric ripple, Bottom: Symmetric ripple. From Ref. 104.

they do not need to be chiral. The asymmetric ripple state is closely related to the structure of the symmetric ripple state (which had not yet been observed in simulations). Our results prompted us to propose a new structural model for the two ripple states, which is shown in Fig. 7, superimposed onto experimental electron density maps (EDM) by Sengupta *et al.* [113]
After the publication of our results, other authors found similar structures with a different generic model.[114] It should be noted, however, that not all generic models produce them. A rather different modulated phase which is less compatible with the EDMs has been reported from simulations of a coarse-grained membrane with soft DPD interactions.[115] Packing effects hence seem to play a role in stabilizing the specific structure(s) of the experimental ripple phase. Indeed, our simulations indicate that one major player is the *splay* of the lipids within the monolayers,[104] *i. e.,* the variations of the local nematic order, which is sustained by packing effects.

Interactions with membrane proteins
Based on this successful membrane model, we proceeded to study interactions of membranes with nanosized inclusions. The idea is, of course, that these inclusions would be generic models for transmembrane (integral) proteins. Membrane-protein interactions have been the subject of considerable theoretical work in the past decades, often based on elastic approaches. The work described below aimed at testing such theories, rather than describing a particular protein. We considered the infinite-dilution limit, where proteins are sparse in the membrane. At finite concentrations, integral proteins may alter the membrane properties (*e.g.*, membrane thinning[116–118]), which will in turn influence the membran-protein interactions.
Many theories for inclusion-membrane interactions were worked out for the case of

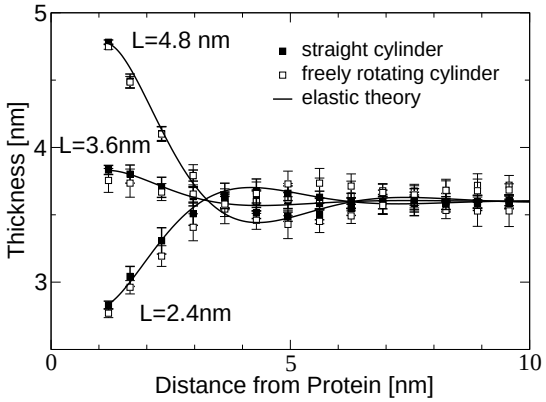

Figure 8: Thickness profiles around inclusion for straight cylinders (closed symbols) and freely rotating spherocylinders (open symbols) compared with elastic theory, for hydrophobically matched inclusion (L = 3.6nm) and inclusions with positive and negative hydrophobic mismatch (L = 4.8nm and L = 2.4nm, respectively). After Ref. 106.

cylindrical inclusions, *i. e.,* cylinders with orientation in the direction of the bilayer normal. They are taken to represent simple helical proteins, such as gramicidin. One frequently addressed question relates to the distortion (compression/expansion) of membranes in the vicinity of hydrophobic cylinders that are longer or shorter than the the membrane thickness. Such 'hydrophobic mismatch' supposedly leads to membrane-induced interactions between inclusions, which may induce clustering.[119] The effect has been verified experimentally with systematic studies of gramicidin[120] and synthetic model peptides.[121, 122] We shall not review the huge amount of theoretical literature here. A list of references with brief discussion is given in Ref. 106.

We have modeled our "protein" in two different ways – as straight, infinitely long cylinder with a hydrophobic section of given length L (corresponding to the situation usually studied in theoretical work), and as freely rotating hydrophobic cylinder of finite length L with hydrophilic semi-spherical caps at both ends. The diameter of the cylinder was chosen 1.8nm such that it roughly matches that of a β-helix (*e. g.,* gramicidin). We should mention that other simulation studies of hydrophobic mismatch interactions between cylindrical inclusions have been published very recently,[123, 124] which however did not include the quantitative comparison with theory on which our work focusses.

As main reference theory, we use here the elastic model that has served us so well to account for the fluctuations of pure bilayers, supplemented with boundary conditions on the bilayer thickness and the curvature of the thickness profile at the

surface inclusion[105,125] (see Ref. 106 for a physical motivation of this particular choice of boundary conditions). First we consider the bilayer thickness distortion around a single inclusion. Fig. 8 shows some corresponding radial profiles. The results for the two protein models are almost identical, and they can be fitted very nicely by the elastic theory.

Next we examine the potential of mean force (pmf) $w(r)$ between two inclusions. It is given by $w(r) = -k_B \ln g(r)$ with the Boltzmann factor k_B and the pair correlation function $g(r)$. The latter has been determined from simulations of a system containing two inclusions by a combination of umbrella sampling and reweighting methods. Some results are shown in Fig. 9. As before, the curves for the two protein models are almost identical, except at very close distances where the two proteins are in direct contact (the corresponding data are outside of the range of the figure). The pmf has an oscillatory component, which can be explained by lipid packing effects. For hydrophobically mismatched inclusions, this packing interaction is superimposed by an additional smooth attractive interaction, which we identify with the hydrophobic mismatch interaction. At small protein distances, the shape of the latter is compatible with the prediction of the elastic theory. At larger distances, the theory predicts a weak oscillatory behavior (with a wavelength much larger than that of the packing interaction), which is not observed in the simulations. The oscillations in the theory can be traced back to a soft peristaltic membrane mode (see the peak of $\langle |t(q)|^2 \rangle$ in Fig. 5), which also leaves a clear oscillatory signature in the thickness profiles (Fig. 8, see also Refs. 126, 127). Apparently, the effect of this mode on the lipid-mediated interactions is destroyed.

4. Conclusions and Outlook

Studying amphiphilic systems with generic models has a long-standing tradition. We hope that our brief review has given a taste of the power of this approach. It is not only highly valuable for investigating large-scale properties of amphiphilic systems, which have been the traditional target of generic modeling, it can also be used to address open questions regarding the properties of membranes on molecular scales.

Specifically, we have discussed the use of generic models to study membrane structure and membrane phase transitions, the statics and kinetics of self-assembly, and also to test the validity of continuum theories against simulations of (coarse-grained) molecular systems. This last aspect is particularly important because it bridges between generic models that represent different levels of coarse-graining. Continuum theories are usually constructed heuristically based on symmetry considerations, and guided by the idea that they should be as simple as possible. They are genuinely generic at the continuum level. Generic molecular models can be used

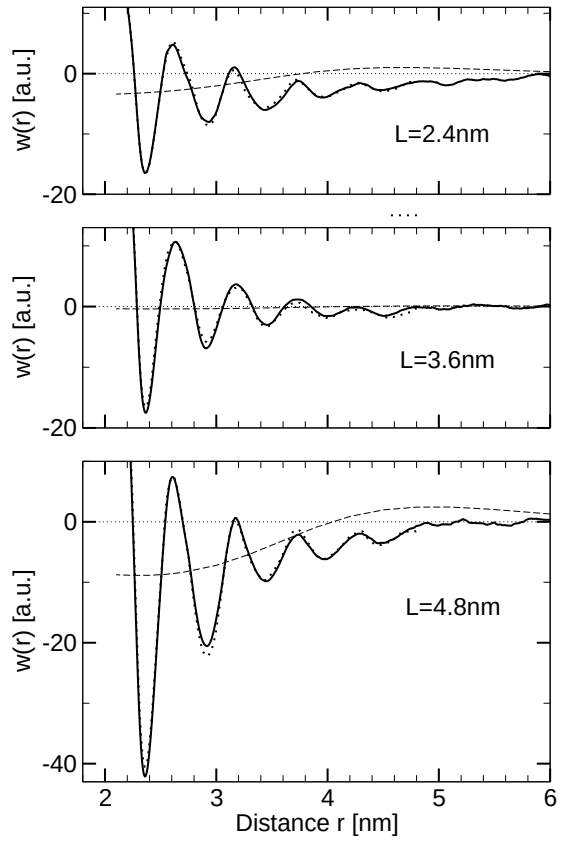

Figure 9: Potential of mean force (pmf) $w(r)$ between inclusions as a function of inclusion distance for straight cylinders (closed lines) and freely rotating spherocylinders (dotted lines). Thin dashed lines show the prediction of the elastic theory. After Refs.106, 128.

to test their validity and their limitations. Bridging between different generic levels could eventually result in a "generic multiscale approach", where generic models at different coarse-graining levels are used concertedly to study non-specific properties and universal processes in amphiphilic systems or other complex materials.

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the John-von Neumann computing center (Jülich), and at the center for parallel computing PC^2 (Paderborn).

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